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Do We Need to Administer Fludrocortisone in Addition to Hydrocortisone in Adult Patients With Septic Shock? An Updated Systematic Review With Bayesian Network Meta-Analysis of Randomized Controlled Trials and an Observational Study With Target Trial Emulation*

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OBJECTIVES: This systematic review and Bayesian network meta-analysis evaluated the efficacy and safety of hydrocortisone combined with fludrocortisone or hydrocortisone alone, compared with placebo in adult patients with septic shock.

DATA SOURCES: By extending a prior Cochrane review, databases, including PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov, along with other relevant websites, were searched until August 31, 2023.

STUDY SELECTION: Randomized controlled trials (RCTs) and observational studies using target trial emulation were included.

DATA EXTRACTION: The primary outcome was short-term mortality with an emphasis on 28- or 30-day mortality as the main measure and in-hospital or ICU mortality as the nearest surrogate of this measure. Three of the most common adverse events, namely, gastroduodenal bleeding, superinfection, and hyperglycemia, were also considered.

DATA SYNTHESIS: A total of 19 studies involving 95,841 patients were included. Hydrocortisone plus fludrocortisone showed the lowest short-term mortality versus placebo (odds ratio [OR]: 0.79; 95% credible interval [CrI], 0.64–0.99; number needed to treat [NNT]: 21, range: 12–500; low certainty of evidence) in terms of informative priors. The surface under the cumulative ranking curve values for hydrocortisone plus fludrocortisone, hydrocortisone alone, and placebo were 0.9469, 0.4542, and 0.0989, respectively. Consistent results were observed in RCTs alone and those using a daily 200-mg dose of hydrocortisone. Although gastroduodenal bleeding or superinfection showed no clear increase, hyperglycemia risk increased. The ORs were 0.53 for placebo versus hydrocortisone plus fludrocortisone and 0.64 for placebo versus hydrocortisone alone, with very low certainty of evidence.

CONCLUSIONS: In adults with septic shock, hydrocortisone plus fludrocortisone improved short-term survival with minimal adverse events compared with hydrocortisone alone or placebo. However, these findings are not definitive due to the limited certainty of evidence and wide NNT range. Additional large-scale, placebo-controlled RCTs are needed to provide conclusive evidence.

KEYWORDS: corticosteroids; fludrocortisone; hydrocortisone; mineralocorticoids; network meta-analysis; septic shock

Despite the implementation of aggressive treatment approaches, septic shock continues to exhibit high mortality rates exceeding 30% in numerous studies (1). This is mainly result from activation

***See also p. 678.**

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KEY POINTS

Question: Is administering fludrocortisone in addition to hydrocortisone to adult patients with septic shock necessary?

Findings: We conducted an updated systematic review using Bayesian network meta-analysis to evaluate the efficacy and safety of hydrocortisone plus fludrocortisone, hydrocortisone alone, or placebo in adult patients with septic shock. Among the tested therapies, hydrocortisone plus fludrocortisone showed the highest likelihood of improving short-term survival.

Meaning: On the basis of the aforementioned evidence, the combined administration of hydrocortisone and fludrocortisone may be considered for adult patients with septic shock.

of proinflammatory and procoagulant pathways (2). Corticosteroids have been considered as a potential strategy for modulating the dysregulated immune response associated with septic shock.

Growing concerns among intensivists are centered around critical-illness-related corticosteroid and mineralocorticoid deficiencies (3, 4). The International Guideline of Surviving Sepsis Campaign conditionally recommended administration of IV hydrocortisone at a typical dose of 200 mg/d to adult patients with septic shock necessitating vasopressor support (5). However, the 2020 Japanese Clinical Practice Guidelines for Sepsis and Septic Shock proposed the adjunctive use of fludrocortisone with hydrocortisone (6) based on a meta-analysis of two randomized controlled trials (RCTs) (7). The differences between these two recommendations warrant a thorough evaluation.

Hydrocortisone possesses glucocorticoid and mineralocorticoid properties. Fludrocortisone, a synthetic mineralocorticoid, is used to substitute for endogenous aldosterone under conditions of absent or insufficient endogenous synthesis. The comparative activity of hydrocortisone to that of fludrocortisone is approximately 1 to 125–150, a ratio that is primarily derived from the effects of hydrocortisone and fludrocortisone on sodium retention in the kidney (8, 9). Differences in the mineralocorticoid effects of hydrocortisone and fludrocortisone beyond this point have been reported in numerous investigations. In patients with sepsis, mineralocorticoid steroidogenesis is more impaired than glucocorticoid synthesis, and this deficiency is associated with sepsis nonsurvival (10). Therefore, the potential benefits of fludrocortisone in treating septic shock are beginning to be highly valued and are believed to stem from the restoration of homeostasis and augmentation of innate immunity (11). Thus, rigorously assessing the combined use of fludrocortisone and hydrocortisone in treating septic shock in adults is imperative.

MATERIALS AND METHODS

Literature Search Strategy

For assessing the efficacy and safety of hydrocortisone plus fludrocortisone, hydrocortisone alone, and placebo in adult patients with septic shock, we conducted a systematic review with network meta-analysis (NMA) by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guideline (12). Our research protocols were registered on INPLASY (registration number: INPLASY202360053, https://inplasy.com/inplasy-2023-6-0053/) and were updated on July 30, 2023, and August 31, 2023. By drawing from a Cochrane review (12), investigators P.C.L. and Y.T.H. searched databases, such as PubMed, Embase, Cochrane Library, and ClinicalTrials.gov, along with other relevant websites until August 31, 2023. We used free text and medical subject headings with keywords, such as "septic shock," "hydrocortisone," and "fludrocortisone," without language restriction. Only parallel RCTs and observational studies with target trial emulation (TTE) were included. Discrepancies were addressed through group consensus.

Study Eligibility and Exclusion Criteria

We included studies based on the following criteria: 1) population: critically ill adults with septic shock, 2) exposure: administration of hydrocortisone with or without fludrocortisone, or placebo, and 3) outcome: data on 28- or 30-day mortality, in-hospital and ICU mortality, or adverse events. We excluded: 1) reviews and case reports/series, 2) studies on sepsis without shock or vasopressor usage, 3) pediatric studies, 4) studies with data insufficient for meta-analysis, and 5) articles with unavailable full texts.

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Risk-of-Bias Assessments

P.C.L. and Y.T.H. also assessed the quality of RCTs by using the revised Cochrane Risk of Bias (RoB 2.0) tool (13). Quality assessment was performed on non-RCT literature by applying the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool (14). Any discrepancies were resolved through group consensus. The results from RoB 2.0 and ROBINS-I were illustrated using the Risk-of-Bias Visualization tool (15).

Data Extraction and Outcome Measures

Two investigators (P.C.L. and Y.T.H.) independently extracted data, capturing study details and treatment strategies. Our primary focus is short-term mortality, specifically, 28- or 30-day mortality. In the absence of short-term mortality data, in-hospital or subsequent ICU mortality was used as the closest available surrogate for assessing patient outcomes. We also evaluated the three main adverse poststeroid administration events: gastroduodenal bleeding, superinfection, and hyperglycemia.

Statistical Analysis

We used NetMetaXL, V.1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada) alongside WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, and Imperial College, London, United Kingdom) adopting a Bayesian method with 10,000 simulations and a random-effects model with informative priors (16). Our sensitivity analysis used vague priors. Subgroup analysis focused on: 1) RCTs exclusively and 2) RCTs using 200 mg/d hydrocortisone as per the Surviving Sepsis Campaign guideline. Treatment effects were presented as odds ratios (OR) with 95% credible intervals (CrIs). Treatment rankings were obtained from surface under the cumulative ranking curve analysis (SUCRA), with high values denoting good outcomes.

Certainty of Evidence Assessment

We appraised evidence certainty for all outcomes by using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Working Group guideline for NMA (17) and the guideline for integrating RCTs and non-RCTs in evidence syntheses (18). We performed grading with GRADEpro software (gradepro.org). The number needed to treat (NNT) for short-term mortality was derived from the absolute risk reduction presented in the GRADE table.

RESULTS

Study Selection and Characteristics

By following the PRISMA 2020 flow diagram and as detailed in **Figure 1**, we identified 17 RCTs through a Cochrane systematic review (12). We excluded two studies that were available only as abstracts (19, 20), one with a cross-over design (21), and one focusing on severe sepsis without septic shock (22). Our final analysis comprised 13 RCTs assessing low doses of hydrocortisone versus placebo (23–35) and three assessing hydrocortisone plus fludrocortisone versus placebo (36–38). Additionally, we included one RCT (39) and a TTE-based cohort study (40) to assess the efficacy of hydrocortisone plus fludrocortisone versus hydrocortisone alone. We also identified a three-armed RCT (41). The detailed summaries and maps of these studies are presented in **Supplementary Tables 1** and **2** (http://links.lww.com/CCM/H472), respectively.

Risk-of-Bias Assessments

The overall risks of bias were rated as high, of some concern, and low in 4, 2, and 12 RCTs, respectively (**Supplementary Fig. 1*A***, http://links.lww.com/CCM/H472). The risk of attrition bias was rated as high in one RCT (30). Three RCTs were assigned a high overall risk of bias due to risk of some concern in two domains (23, 28, 31). The cohort study using TTE was evaluated as having a serious risk of bias due to the moderate risk present in three domains (**Supplementary Fig. 1*B***, http://links.lww.com/CCM/H472).

Primary Outcome: Short-Term Mortality

Data from 19 studies and 95,841 patients (shown in **Fig. 2*A***) revealed that hydrocortisone plus fludrocortisone reduced the risk of short-term mortality. In informative and vague priors, the reduction had an OR of 0.79 (95% CrI, 0.64–0.99) and 0.80 (95% CrI, 0.62–1.00) relative to the placebo. In the comparison of hydrocortisone plus fludrocortisone with hydrocortisone alone, the ORs were 0.85 (95% CrI, 0.67–1.08)

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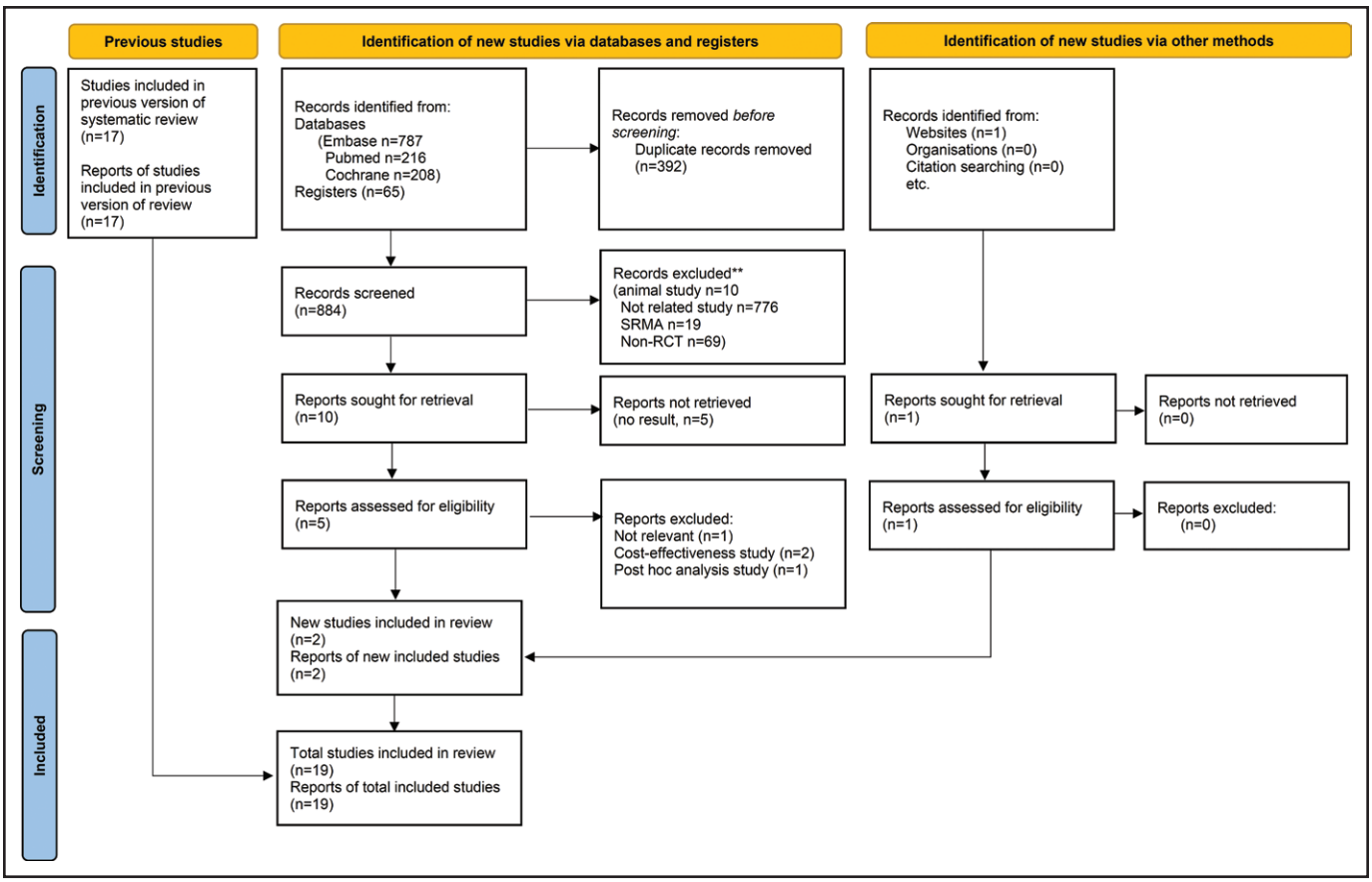
Previous studies
Identification of new studies via databases and registers
Identification of new studies via other methods
Identification
Screening
Included
Studies included in previous version of systematic review (n=17)
Reports of studies included in previous version of review (n=17)
Records identified from: Databases (Embase n=787 Pubmed n=216 Cochrane n=208) Registers (n=65)
Records removed before screening: Duplicate records removed (n=392)
Records identified from: Websites (n=1) Organisations (n=0) Citation searching (n=0) etc.
Records screened (n=884)
Records excluded** (animal study n=10 Not related study n=776 SRMA n=19 Non-RCT n=69)
Reports sought for retrieval (n=10)
Reports not retrieved (no result, n=5)
Reports sought for retrieval (n=1)
Reports not retrieved (n=0)
Reports assessed for eligibility (n=5)
Reports excluded: Not relevant (n=1) Cost-effectiveness study (n=2) Post hoc analysis study (n=1)
Reports assessed for eligibility (n=1)
Reports excluded: (n=0)
New studies included in review (n=2) Reports of new included studies (n=2)
Total studies included in review (n=19) Reports of total included studies (n=19)

Figure 1. Search in accordance with the flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020. RCT = randomized controlled trial, SRMA = systematic review and meta-analysis.

using informative priors and 0.86 (95% CrI, 0.66–1.09) using vague priors. Hydrocortisone plus fludrocortisone appeared to be more effective than hydrocortisone alone. The probability that substantive benefit is absent is small. Hydrocortisone monotherapy exhibited marginal benefits over placebo (OR: 0.93; 95% CrI, 0.79–1.09 using informative and vague priors). The SUCRA evaluations distinctly favor hydrocortisone plus fludrocortisone (score: 0.9469) over hydrocortisone alone (score: 0.4542) and placebo (score: 0.0989). The rankogram in **Figure 3*A*** further emphasizes the therapeutic superiority of hydrocortisone plus fludrocortisone.

In accordance with the GRADE Working Group's guideline on integrating evidence from RCTs and non-RCTs, the initial evaluation of evidence derived from RCTs is recommended (18). The forest plots in **Figure 2*B*** and the rankogram in **Figure 3*B*** reveal that the NMA limited to RCTs closely aligns with the results obtained by combining RCTs and cohort studies using TTE. Hydrocortisone plus fludrocortisone is the top treatment choice, with a SUCRA score of 0.9501, surpassing hydrocortisone alone (0.4397) and placebo (0.1102).

The GRADE Working Group advises prioritizing RCTs due to consistent results when determining evidence certainty (18). In contrast to placebo, hydrocortisone plus fludrocortisone and hydrocortisone alone received a low certainty rating (**Supplementary Table 2**, http://links.lww.com/CCM/H472). The main downgrade reason was imprecision (18), with 95% CrIs approaching the minimally important difference threshold (defined as an OR of 0.9) (**Supplementary Table 3**, http://links.lww.com/CCM/H472). The NNT of hydrocortisone plus fludrocortisone compared with placebo was 21, with a range of 12–500.

Figures 2*C* and **3*C*** underscore the superior efficacy of hydrocortisone plus fludrocortisone (SUCRA score: 0.9546) over that of hydrocortisone (0.3693) or placebo (0.1761) in the RCT analysis involving 7432 patients from 15 RCTs using 200 mg/d hydrocortisone.

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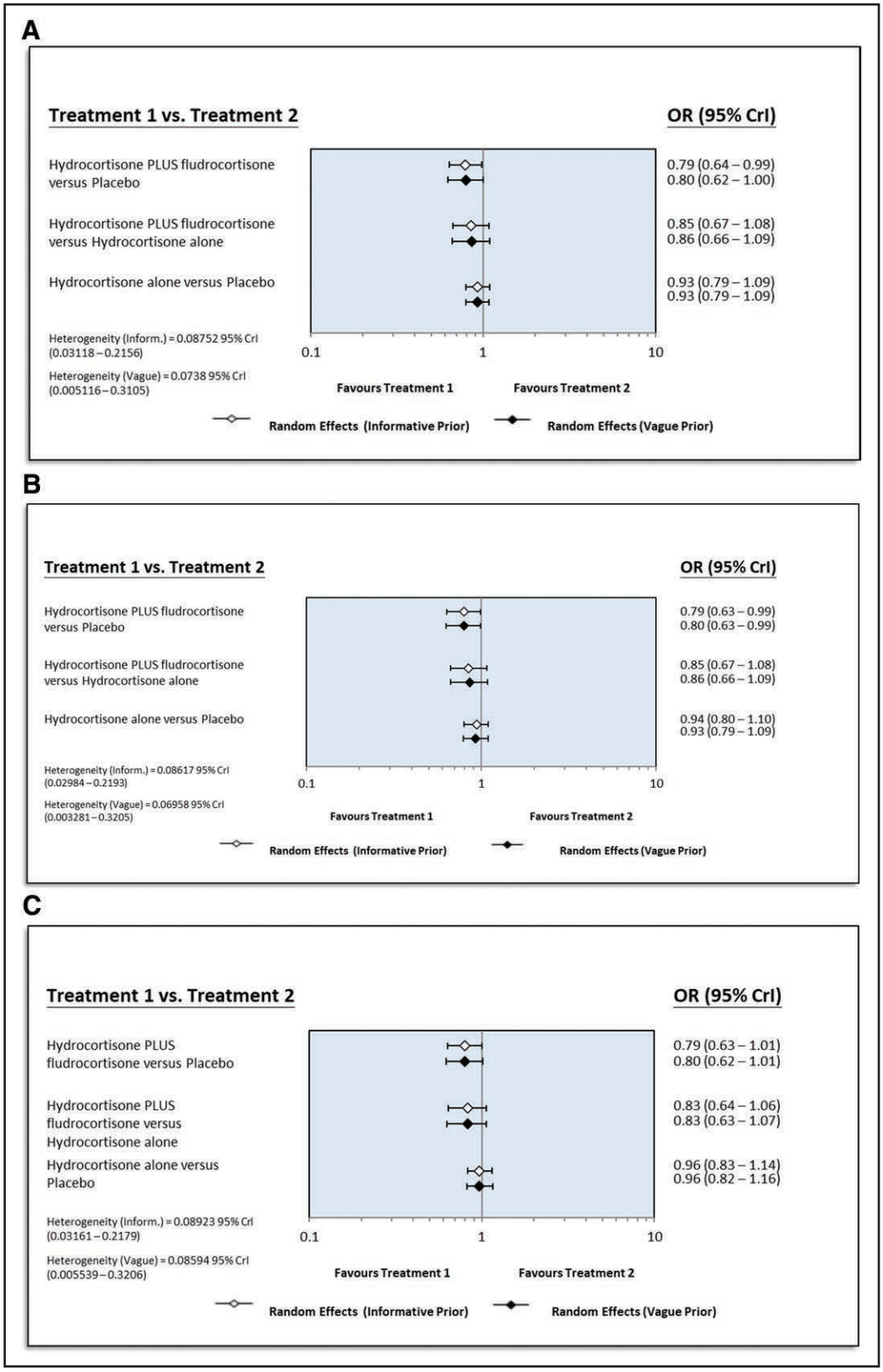
A
Treatment 1 vs. Treatment 2
OR (95% CrI)
Hydrocortisone PLUS fludrocortisone versus Placebo
0.79 (0.64 – 0.99)
0.80 (0.62 – 1.00)
Hydrocortisone PLUS fludrocortisone versus Hydrocortisone alone
0.85 (0.67 – 1.08)
0.86 (0.66 – 1.09)
Hydrocortisone alone versus Placebo
0.93 (0.79 – 1.09)
0.93 (0.79 – 1.09)
Heterogeneity (Inform.) = 0.08752 95% CrI (0.03118 – 0.2156)
Heterogeneity (Vague) = 0.0738 95% CrI (0.005116 – 0.3105)
0.1
1
10
Favours Treatment 1
Favours Treatment 2
Random Effects (Informative Prior)
Random Effects (Vague Prior)
B
Treatment 1 vs. Treatment 2
OR (95% CrI)
Hydrocortisone PLUS fludrocortisone versus Placebo
0.79 (0.63 – 0.99)
0.80 (0.63 – 0.99)
Hydrocortisone PLUS fludrocortisone versus Hydrocortisone alone
0.85 (0.67 – 1.08)
0.86 (0.66 – 1.09)
Hydrocortisone alone versus Placebo
0.94 (0.80 – 1.10)
0.93 (0.79 – 1.09)
Heterogeneity (Inform.) = 0.08617 95% CrI (0.02984 – 0.2193)
Heterogeneity (Vague) = 0.06958 95% CrI (0.003281 – 0.3205)
0.1
1
10
Favours Treatment 1
Favours Treatment 2
Random Effects (Informative Prior)
Random Effects (Vague Prior)
C
Treatment 1 vs. Treatment 2
OR (95% CrI)
Hydrocortisone PLUS fludrocortisone versus Placebo
0.79 (0.63 – 1.01)
0.80 (0.62 – 1.01)
Hydrocortisone PLUS fludrocortisone versus Hydrocortisone alone
0.83 (0.64 – 1.06)
0.83 (0.63 – 1.07)
Hydrocortisone alone versus Placebo
0.96 (0.83 – 1.14)
0.96 (0.82 – 1.16)
Heterogeneity (Inform.) = 0.08923 95% CrI (0.03161 – 0.2179)
Heterogeneity (Vague) = 0.08594 95% CrI (0.005539 – 0.3206)
0.1
1
10
Favours Treatment 1
Favours Treatment 2
Random Effects (Informative Prior)
Random Effects (Vague Prior)

Figure 2. Forest plots presenting the odds ratios for short-term mortality among treatment groups receiving either combined hydrocortisone and fludrocortisone, hydrocortisone alone, or placebo: includes all studies (**A**); has been narrowed down to randomized controlled trials (**B**); and specifically examines randomized controlled trials administering an initial daily hydrocortisone dosage of 200 mg (**C**). CrI = credible interval, OR = odds ratio.

Adverse Events

Gastroduodenal Bleeding. Eight RCTs involving 2023 participants examined gastroduodenal bleeding. The wide 95% CrIs obtained when comparing hydrocortisone plus fludrocortisone with placebo, hydrocortisone plus fludrocortisone with hydrocortisone alone, and hydrocortisone alone with placebo failed to highlight any obvious difference in gastroduodenal bleeding risk among these treatments (**Supplementary Fig. 2*A***, http://links.lww.com/CCM/H472). The certainty of evidence was assessed as very low (**Supplementary Table 4**, http://links.lww.com/CCM/H472). In the rankogram in **Supplementary Figure 2*B*** (http://links.lww.com/CCM/H472), hydrocortisone plus fludrocortisone ranked the lowest among all treatments for the occurrence of gastroduodenal bleeding. In terms of SUCRA scores, hydrocortisone plus fludrocortisone (0.7052) had a similar rank as placebo (0.6758), but was notably ranked higher than hydrocortisone alone (0.119). This

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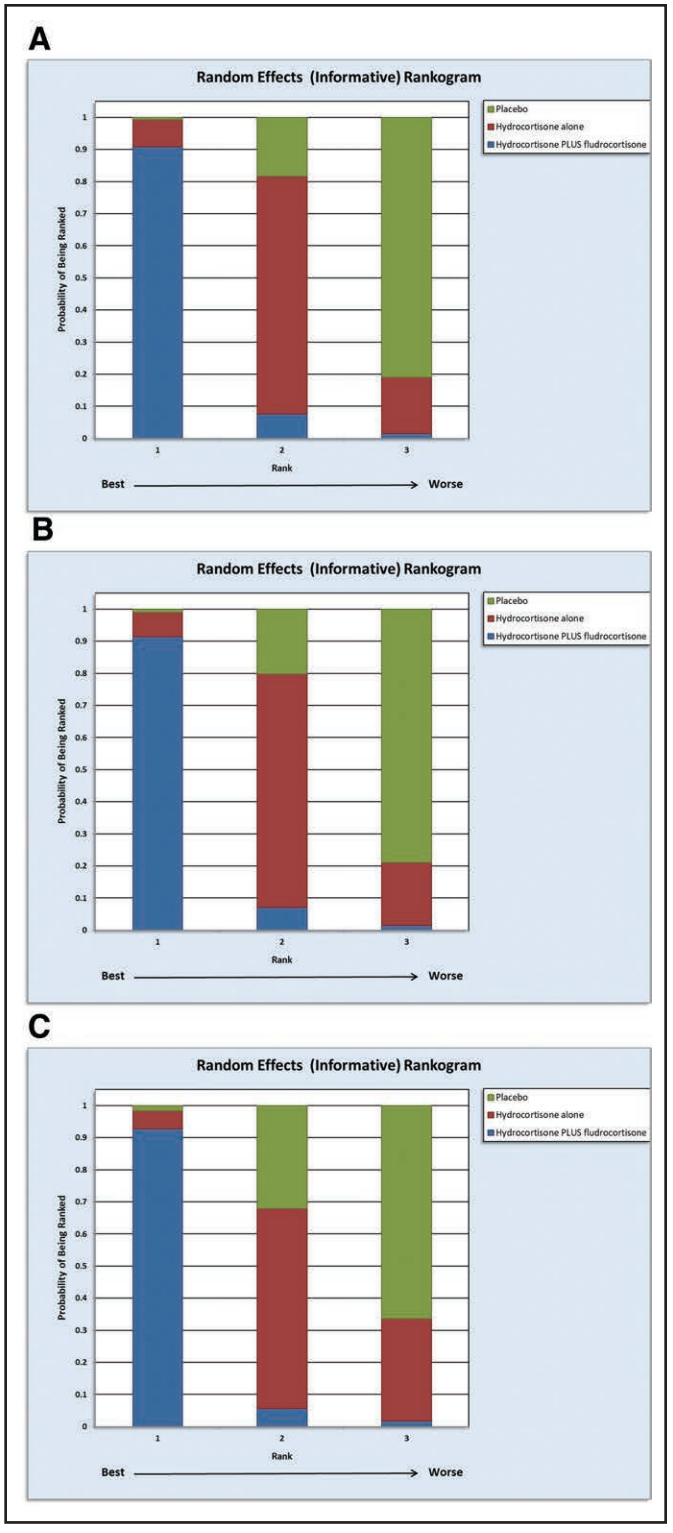

Figure 3. Rankogram illustrating the probability rankings for improving short-term mortality across treatments: combined hydrocortisone and fludrocortisone, hydrocortisone alone, or placebo: encompasses all studies (**A**); is limited to randomized controlled trials (**B**); and highlights randomized controlled trials starting with a daily hydrocortisone dose of 200 mg (**C**).

result suggests that hydrocortisone plus fludrocortisone could be the least favorable option when considering the risk of gastroduodenal bleeding.

Superinfection. The same eight RCTs involving 2023 participants were included in the NMA for the risk of superinfection. Once again, the expansive 95% CrIs in forest plots illustrating the comparison of hydrocortisone plus fludrocortisone with placebo, hydrocortisone plus fludrocortisone with hydrocortisone alone, and hydrocortisone alone with placebo, suggest the absence of a clear distinction in superinfection rates (**Supplementary Fig. 3*A***, http://links.lww.com/CCM/H472) with a very low certainty of evidence (**Supplementary Table 5**, http://links.lww.com/CCM/H472). In the rankogram in **Supplementary Figure 3*B*** (http://links.lww.com/CCM/H472), placebo, followed by hydrocortisone plus fludrocortisone, ranked the lowest for the occurrence of superinfection. In accordance with SUCRA scores, placebo (0.7522) showed a slightly higher ranking than hydrocortisone plus fludrocortisone (0.5964) and apparently ranked higher than hydrocortisone alone (0.1514). This result hints that hydrocortisone plus fludrocortisone might not elevate superinfection risk.

Hyperglycemia. In seven RCTs involving 5365 patients assessing hyperglycemia risk, the placebo group had a lower likelihood for hyperglycemia than the hydrocortisone plus fludrocortisone group (OR: 0.53 [95% CrI, 0.37–0.73] using informative priors, **Supplementary Fig. 4*A***, http://links.lww.com/CCM/H472) with moderate evidence certainty (**Supplementary Table 6**, http://links.lww.com/CCM/H472). The comparison between hydrocortisone alone and hydrocortisone plus fludrocortisone revealed broad CrIs (OR: 0.82 [95% CrI, 0.48–1.37] using informative priors; additional details in Supplementary Fig. 4*A*, http://links.lww.com/CCM/H472). The comparison of placebo with hydrocortisone alone showed that the former had decreased odds for hyperglycemia (OR: 0.64 [95% Crl, 0.42–0.96]) albeit with very low evidence certainty (Supplementary Table 6, http://links.lww.com/CCM/H472). SUCRA scores and rankograms consistently showed that among the investigated therapies, hydrocortisone plus fludrocortisone, which had the lowest score of 0.1073, might be the most likely to cause hyperglycemia. Among the investigated therapies, hydrocortisone alone was the next

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most likely to cause hyperglycemia with a score of 0.4003, and placebo had the least likelihood to cause hyperglycemia with a score of 0.9924 (**Supplementary Fig. 4*B***, http://links.lww.com/CCM/H472).

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DISCUSSION

Our NMAs show that hydrocortisone plus fludrocortisone improves short-term mortality outcomes for septic shock in adults, whereas hydrocortisone alone has limited effects. Mineralocorticoids have roles beyond sodium retention. Heming et al (42) have highlighted how these substances affect immune responses, which we discuss further below. Different mineralocorticoid receptor (MR) isoforms exist. Some bind to glucocorticoids and mineralocorticoids, whereas others bind only to mineralocorticoids. The deactivation of glucocorticoids by 11β-hydroxysteroid dehydrogenase ensures that mineralocorticoids have strong MR interactions. Additionally, MRs are present in immune cells, and their activation enhances leukocyte adhesion, aiding in bacterial infection eradication. Experimental sepsis studies have also demonstrated that mineralocorticoids reduce the plasma levels of histamine, serotonin, and bradykinin, thereby accelerating the reversal of shock. These findings support the conclusion that hydrocortisone plus fludrocortisone is the most effective treatment for improving short-term mortality, as evidenced by our NMA results.

A recent study performed a fixed-effects NMA using a frequentist approach to compare hydrocortisone administered as an IV bolus or via continuous infusion with hydrocortisone plus fludrocortisone (43). Consistent with our data, the combination reduced 90-day all-cause mortality compared with the control, yielding a risk ratio (RR) of 0.88 (95% CI, 0.81–0.97). We did not assess long-term mortality due to the myriad factors influencing septic shock in adults. The potential of hydrocortisone plus fludrocortisone to improve 90-day mortality further strengthens the case for its use in adult patients with septic shock. We used a Bayesian approach in our statistical analysis because of its strong alignment with clinical reasoning. Bayesian analysis has been recognized as a practical methodology for interpreting clinical trials and formulating clinical practice guidelines (44). Direct comparisons between hydrocortisone plus fludrocortisone and hydrocortisone alone are limited. In our NMA, we identified only two RCTs and one TTE-style study. By using indirect data from the network of studies that compared hydrocortisone plus fludrocortisone and hydrocortisone alone with placebo, we strengthened the evidence base for comparing the two treatment options directly. Our NMA results demonstrate that hydrocortisone plus fludrocortisone is more likely to reduce short-term mortality than hydrocortisone alone as indicated by the 95% CrIs and SUCRA values. The aforementioned frequentist NMA (43) included only a single RCT that compared the combination regimen with hydrocortisone alone. Generally, large sample sizes enhance study power by providing clear effect size estimates and minimizing chance results, a principle that is equally applicable to (network) meta-analysis (45). A notable feature of our NMA is the inclusion of a three-armed RCT (41) and a recent cohort study (88,275 patients) with TTE (40). The use of TTE in observational studies stimulates researchers to formulate research questions for hypothetical RCTs that compare drug effectiveness (46). Therefore, we believe that enrolling an increased number of cases in this topic will lead to pooled estimates with increased precision.

Our findings indicate that hydrocortisone alone demonstrated marginal benefits over placebo. In a systematic review conducted in 2019, Siddiqui et al (47) concluded that the administration of hydrocortisone significantly reduced the 28-day mortality rate among patients with refractory septic shock. However, their results were based on a meta-analysis of only five RCTs. Systematic reviews with meta-analyses published after 2018 have shown inconsistent results regarding short-term mortality linked to hydrocortisone use in patients with sepsis (12, 47–50). These disparities may arise from factors, such as the use of different steroids, application of varied statistical methods, and inclusion of participants beyond just adults with septic shock. Of course, the effect of hydrocortisone alone may be minimal, which might cause fluctuations in the results under the influence of the aforementioned covariates. Pirracchio et al (43) reported a patient-level meta-analysis of low-dose hydrocortisone therapy in patients with septic shock. The comparison of hydrocortisone with placebo by using individual patient data (IPD) yielded marginal results with an RR of 0.93 and 95% CIs of 0.82–1.04 for 90-day mortality. IPD meta-analysis typically yields considerable enhancements

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in the quantity and quality of data through increased statistical power, the ability to adjust for confounding factors, broadened analytical possibilities, and the generation of results with increased comprehensiveness and robustness (51). The results mentioned above are consistent with the findings of our Bayesian NMA. This consistency prompts us to reconsider whether the guidelines for the treatment of septic shock in adults should be revised to recommend the use of hydrocortisone plus fludrocortisone instead of hydrocortisone alone.

Previous Bayesian NMAs have suggested that a daily dosage of 200–400 mg of hydrocortisone or equivalent steroids is likely to provide the greatest benefit to patients with sepsis (52). We also attempted to analyze the effect of various corticosteroids on short-term mortality by using NMA. We identified only two additional three-armed RCTs comparing dexamethasone, methylprednisolone, and placebo that were published in 1976 (53) and 1984 (54). These studies are limited by their methodologies, which are outdated relative to current critical care practices. Thus, caution is advised when interpreting the NMA results indicating potential short-term mortality benefits from dexamethasone and methylprednisolone treatments due to intransitivity concerns (**Supplementary Fig. 5**, http://links.lww.com/CCM/H472).

Our study has limitations. First, we only considered adults. Whether different corticosteroids have varying effects on pediatric patients with septic shock cannot be determined from our study. If RCTs examining fludrocortisone alone exist, then conducting a component NMA could provide an in-depth understanding of the roles of fludrocortisone in septic shock management. It is worth noting that most of the RCTs investigating hydrocortisone plus fludrocortisone originated from the same group and geographic region. Expanding research to include studies from diverse regions and research teams is crucial for a more comprehensive understanding of the efficacy and generalizability of this treatment strategy. Furthermore, we excluded certain outcomes, such as time to wean off vasopressors, ICU stay length, ventilator-free days, and kidney replacement needs, given their variability based on institutional practices. Another constraint was our focus on just three adverse events of high prevalence because events with low incidences can reduce the robustness of NMA results. Notably, we found elevated risks of hyperglycemia under treatments with hydrocortisone plus fludrocortisone and hydrocortisone alone. Assessing the effect of steroid-induced hyperglycemia through NMA remains challenging.

CONCLUSIONS

In adults with septic shock, hydrocortisone plus fludrocortisone improves short-term survival with an increased risk of hyperglycemia. Given the affordability and accessibility of fludrocortisone, its coadministration with IV hydrocortisone is an appropriate option for patients receiving enteral nutrition. Nevertheless, the uncertainty and wide NNT range for short-term mortality underscore the urgent need for well-conducted, triple-blinded RCTs to provide clear guidance.

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